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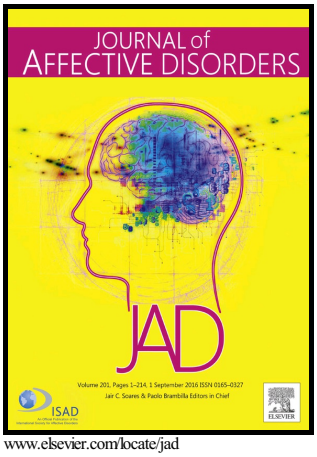

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Thyroid peroxidase antibodies during early gestation and the subsequent risk of first-onset postpartum depression: a prospective cohort study

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Abstract:

Background:

During the postpartum period, women are at risk for new onset of both auto-immune thyroid disorders and depression. The presence of thyroid peroxidase antibodies (TPO-ab) during early gestation is predictive for postpartum auto-immune thyroid dysfunction. The aim of this study was to investigate the association between TPO-ab status during early gestation and first-onset postpartum depression.

Methods:

Prospective cohort study (n=1075) with follow-up during pregnancy up to one year postpartum. Thyroid function and TPO-ab status were measured during early gestation. Depressive symptomatology was assessed during each trimester and at four time points postpartum with the Edinburgh Depression Scale (EDS). Women with antenatal depression were not eligible for inclusion. Self-reported postpartum depression was defined with an EDS cut-off of ≥13.

Results:

The cumulative incidence of self-reported first-onset depression in the first postpartum year was 6.3%. A positive TPO-ab status was associated with an increased risk for self-reported first-onset depression at four months postpartum (adjusted OR 3.8; 95% CI 1.3-11.6), but not at other postpartum time points. Prevalence rates of self-reported postpartum depression

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declined after four months postpartum in the TPO-ab positive group, but remained constant in the TPO-ab negative group.

Limitations:

Depression was defined with a self-rating questionnaire (EDS).

Conclusions:

Women with an increased TPO-ab titer during early gestation are at increased risk for self-reported first-onset depression. The longitudinal pattern of self-reported postpartum depression in the TPO-ab positive group was similar to the typical course of postpartum TPO-ab titers changes. This suggests overlap in the etiology of first-onset postpartum depression and auto-immune thyroid dysfunction. Thyroid function should be evaluated in women with first-onset postpartum depression.

Keywords: TPO-ab; pregnancy; postpartum depression; EDS; onset timing; thyroid dysfunction

Introduction

Postpartum depression is a disabling and heterogeneous disorder with a huge variety in biological, psychological and social risk factors (Howard et al., 2014). In addition, there is substantial difference in the onset timing, severity and course of postpartum depression (Putnam et al., 2017) (Fisher et al., 2016). The most important risk factor for postpartum depression is a depressive episode earlier in life or during pregnancy. In a large study among women with postpartum depression, approximately 60% of women reported an onset of their episode before pregnancy or during the antenatal period (Wisner et al., 2013).

Antenatal depression occurs during an entirely different immune and endocrine state than postpartum depression and may therefore have a different origin (Osborne and Monk, 2013). Interestingly, the postpartum period is a high risk period for more severe and first-onset episodes of depression (Munk-Olsen et al., 2016). Therefore, it is important to consider onset timing when studying risk factors for postpartum depression (Wisner et al., 2013).

The postpartum period is also associated with an increased risk for the new onset of auto-immune thyroid disorders (Andersen et al., 2016). The presence of thyroid peroxidase antibodies (TPO-ab) during early gestation is a clear marker for the occurrence of postpartum auto-immune thyroid dysfunction, induced by the typical postpartum rebound phenomena of

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TPO-ab titers (Balucan et al., 2013; Fung et al., 1988; Jansson et al., 1984; Stagnaro-Green et al., 1992). Interestingly, TPO has also been named as a predictor for postpartum depression (Dama et al., 2016).

Four studies reported an association between an increased TPO-ab titer during early gestation and depression postpartum (Groer and Vaughan, 2013; Harris et al., 1992; Kuijpens et al., 2001; Lazarus et al., 1996). However, none of these studies focused on first-onset depression and three out of four studies did not take into account antenatal depression (Groer and Vaughan, 2013; Harris et al., 1992; Lazarus et al., 1996), while one study only briefly mentioned this in a sub analysis (Kuijpens et al., 2001). Together, as acknowledged by Dama and colleagues in their recent review, in previous studies antenatal depression may have confounded the association between a TPO-ab positive status during pregnancy and postpartum depression (Dama et al., 2016). Accordingly, the current study was designed to investigate the association between a positive TPO-ab status during early gestation and first-onset postpartum depression. We hypothesized that women are particularly at increased risk for first-onset depression three to four months postpartum, during the typical rebound of TPO-ab titers.

Method

Participants

Participants were included in the Holistic Approach to Pregnancy and the first Postpartum year (HAPPY) study, a large prospective cohort that is described in detail elsewhere (Truijens et al., 2014). In sum, the HAPPY-study focuses on maternal wellbeing during pregnancy and the postpartum period. During a recruitment period of 18 months (2013-2014), Dutch-speaking pregnant women were informed about the study during their first trimester appointment at 17 community midwives offices in the South-East of the Netherlands. Women with a non-singleton pregnancy or history of a severe psychiatric disorder were not eligible for inclusion. We excluded women with a self-reported lifetime history of depression as well as all women with depression during the full course of their pregnancy. In addition, women with a known thyroid disease at baseline as well as other endocrine/auto-immune disorders were not eligible for inclusion. The HAPPY-study was approved by the Medical Ethical Committee of the Maxima Medical Centre Veldhoven and the Psychology Ethics Committee of Tilburg University (protocol number EC-2012.25).

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Data collection, procedures and definitions

This study is reported in line with the STROBE guidelines (von Elm et al., 2007). Questionnaires were used to collect baseline demographic information, as well as relevant medical, obstetric, psychological and lifestyle data. If applicable, data were verified with medical records. Standardized blood measurements were performed at 10-12 weeks gestation and included TPO-ab, as well as thyroid releasing hormone (TSH) and free thyroxine (FT4). Measurements were performed in Li-heparin plasma using electrochemoluminescence assays (Cobas® e 601, Roche Diagnostics, Mannheim Germany). We defined a positive TPO-ab status with the commonly used threshold of >20 IU/ml (Prummel and Wiersinga, 2005). This cut-off is probably not appropriate throughout the full course of pregnancy (Dama et al., 2016). Therefore, we performed the TPO-ab measurement during early pregnancy, before downsizing of maternal auto-immune processes emerges (Balucan et al., 2013).

Depressive symptomatology was assessed repeatedly every trimester and four times during the postpartum period (6 weeks, and 4, 8, and 12 months) using the Edinburgh Depression Scale (EDS). The EDS is validated to detect women with a high probability of major depression both during pregnancy and postpartum. In this study, self-reported depression was defined with the following validated EDS cut-off scores: trimester 1, ≥11; trimester 2 and 3, ≥10; (Bergink et al., 2011); postpartum period ≥13 (Cox et al., 1987; Harris et al., 1989; Pop et al., 1992). Women who scored above the trimester cut-offs during the course of their pregnancy were not eligible for inclusion in our study.

Our primary outcome measure was the occurrence of first-onset self-reported depression (i.e. incidence of new cases) at four months postpartum. Women with an increased TPO-ab titer during early gestation show a subsequent decline of their titer throughout pregnancy, with a typically rebound between three to five months postpartum and a gradual decline afterwards (Fung et al., 1988; Jansson et al., 1984; Stagnaro-Green et al., 1992). Therefore we considered four months postpartum to be the most optimal time point available to assess a possible association between a positive TPO-ab status during early gestation and the occurrence of first-onset self-reported depression postpartum. First-onset self-reported depression at other postpartum time points (6 weeks, 8 and 12 months) were used as secondary outcome measures.

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Statistical methods

SPSS (version 24, IBM) was used for the statistical analyses. Binary logistic regression was used to evaluate the association between TPO-ab status during the first trimester (exposure) and the incidence of new cases of self-reported depression at four months postpartum (primary outcome), and at 6 weeks, 8 months and 12 months postpartum (secondary outcomes). To facilitate interpretation of the results, we plotted point prevalence rates of self-reported postpartum depression (EDS ≥13) over time (at 6 weeks, 4, 8 and 12 months postpartum) according to TPO-status. A multiple logistic regression analysis was performed to adjust for potential confounders. Based on previous literature, we included the following confounding variables: anxiety during pregnancy (Generalized Anxiety Disorder (GAD-7) scale sum score at 12 weeks gestation, continuous), age (years, continuous) and preterm delivery (<37 weeks of gestation, dichotomous) (Dama et al., 2016), primiparity (dichotomous) (Greer et al., 2011; Howard et al., 2014) and recent life-events (self-reported, dichotomous) (Kuijpens et al., 2001). In addition, we considered the following confounding variables: mode of delivery (vaginal delivery or cesarean section), health problems of the baby (self-reported, dichotomous) and social support during the postpartum period (Tilburg Support Scale sum score, continuous). All potential confounding variables were introduced both separately and simultaneously into the unadjusted model to verify a potential effect on our exposure of interest (TPO-ab status). Logistic regression analyses were evaluated with Wald tests (χ^2, distribution, α=0.05). Results are presented with crude and adjusted odds ratio's (OR's) together with corresponding 95% confidence intervals.

Additionally, we tested whether a positive TPO-ab status during pregnancy was associated with differences in mean TSH and FT4 concentrations by using T-tests. TSH data was log-transformed to meet the assumption of normality, and log transformed mean TSH values are reported. Cohen's d are used to report the size of the effect (Cohen, 1988). Finally, we used a sensitivity analysis to assess the robustness of the findings. For this aim, we changed the dichotomous TPO-ab variable into a categorical variable (3 categories: ≤ 20 IU/ml; 21-100 IU/ml; ≥101 IU/ml).

Women were included in the final study sample if 1) at least two out of three pregnancy EDS scores were available and 2) the EDS score at four months postpartum (primar outcome measure) was available.

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As a result of our data selection strategy we did not have any missing data on our primary outcome measure (EDS score ≥13 at 4 months postpartum). During pregnancy, the proportion of missing EDS measures varied between 1.7% to 2.5%. Regarding the secondary outcome measures, the proportion of missing data varied between 8.3% to 23.3%. Missing data was handled with the multiple imputation algorithm as implemented in SPSS version 24 (IBM). Ten imputed datasets were created and all predictor and outcome variables were used for imputation modelling. Analyses were run on the imputed data and pooled estimates are reported (Rubin, 2008). To explore the impact of the imputation procedure on our results, we repeated all analyses using the original dataset.

Results

Study sample

A detailed overview of the participant selection process is presented in Figure 1. In total, n=3160 Dutch-speaking pregnant women were informed about the HAPPY-study, of which 71.8% (n=2269) provided informed consent. A self-reported lifetime history of depression (n=300) and on ore more EDS scores above the trimester specific cut-offs during pregnancy (n=386) were the most important reasons for exclusion. Of the women that were eligible for this study (n=1364), follow-up data at four months postpartum was available for n=1075 (78.8%) women. According to the baseline demographic study characteristics (Table 1), the vast majority of women had the Dutch nationality, a high educational level, a paid job and was married or living together. Most baseline characteristics did not differ substantially between women that were included and excluded because of missing follow-up data during pregnancy or at four months postpartum (n=289, 21.2%). However, excluded women showed a higher prevalence of unplanned pregnancies (7.8% versus 3.7%), preterm delivery (6.6% versus 3.5%), smoking during pregnancy (8.6% versus 2.6%) and a lower prevalence of high education level (50.8% versus 69.3%).

TABLE 1. Baseline characteristics (n=1075)

	mean (SD)	**n (%)**
Age (years)	30.4 (3.5)	
Gestational age (days)	278 (10)	

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Preterm delivery (<37 weeks)	38 (3.5)
Married or living together	1044 (99.0)
High educational level[b]	764 (69.3)
Dutch nationality	1038 (98.4)
Paid job	1014 (96.2)
Primiparous	525 (49.9)
Unplanned pregnancy	39 (3.7)
Smoking during pregnancy	27 (2.6)
Alcohol consumption during pregnancy	13 (1.2)

[a] In case of missing data (maximum n=22), valid percentages are presented
[b] Bachelor and/or master degree

Thyroid measurements and EDS scores during pregnancy

In total, 121 out of 1075 women (11.3%) had a positive TPO-ab status (>20 IU/ml) at 12 weeks of gestation. The median of the positive TPOA-ab measurements was 74.0 IU/ml, with an inter quartile range (IQR) of 29.0 – 170.0. In the full sample, we observed a median TSH blood level of 1.4 mU/L (IQR 1.0-2.1 mU/l) and median FT4 of 14.4 pmol;/L (IQR 13.4-15.4 pmol;/L).

TSH concentrations were significantly higher in the group with a positive TPO-AB status (log-transformed mean 0.3 mU/L, SD 0.4) compared to the group with a negative TPO-ab status (log-transformed mean 0.1 mU/L, SD 0.3); $t(1073) = -4.9$, $p<0.0001$, cohen's $d=0.43$, medium effect size). FT4 concentrations were significantly lower in the group with a positive TPO-AB status (mean 14.2 pmol/L, SD 1.8) than in de group with a negative TPO-ab status (mean 14.6 pmol/L, SD 1.7; $t(1073)=2.2$, $p=0.028$, Cohen's $d=0.23$, small effect size).

We excluded women with an EDS score above the trimester specific cut-offs, which resulted in the following mean EDS scores of the remaining women: trimester 1, 2.7 (SD 2.5); trimester 2, 3.4 (SD 2.6); trimester 3, 3.3 (SD 2.6). Mean EDS-scores did not significantly differ between women with a positive versus negative TPO-ab status during any of the trimesters.

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The association between thyroid peroxidase antibodies status and first-onset postpartum depression

In the total sample, 6.3% (68/1075) of the women fulfilled the definition of self-reported postpartum depression at one or more of the four assessments during the first postpartum year (n=43 once; n=16 twice; n=6 three times; n=3 four times).

At four months postpartum, we observed a risk of self-reported first-onset postpartum depression of 5.0% (6/119) among women with a positive TPO-ab status, compared to 1.5% (14/934) among women with a TPO-ab negative status (crude OR 3.5, 95% CI 1.3–9.4, p=0.016). This effect remained significant after adjustment for potential confounders (see method section) (adjusted OR 3.8, 95% CI 1.3-11.6, p=0.017).

The association between TPO-ab status and self-reported first-onset depression was not significant at 6 weeks, 8 months and 12 months postpartum. The point prevalence rates of self-reported postpartum depression according to TPO-ab status at all postpartum assessments are presented in Figure 2. After a peak of self-reported postpartum depression at four months postpartum among women with a positive TPO-ab status, the point prevalence rates of self-reported postpartum depression linearly declined from 5.8% (7/121) to 0.8% (1/121) at 12 months postpartum. Among women with a negative TPO-ab status, the prevalence rates of self-reported postpartum depression remained relatively constant across all time points in the first postpartum year (2.1%, 20/954 – 3.0%, 29/954). A sensitivity analysis showed that the direction of the association between TPO-ab and self-reported first-onset depression at four months postpartum remained constant after changing our dichotomous exposure TPO-ab status into a categorical covariate (≤ 20 IU/ml; 21-100 IU/ml; ≥101 IU/ml). Repeating the analyses in the original (non-imputed) dataset supported our findings regarding the direction, size and significance of the reported associations.

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Discussion

In this large prospective cohort study including n=1075 women, the cumulative incidence of self-reported first-onset postpartum depression during the first postpartum year was 6.3%. A positive TPO-ab status during pregnancy was associated with a threefold increased risk of self-reported first-onset depression at four months postpartum but not at other postpartum time points. Point prevalence rates of self-reported postpartum depression declined after four months postpartum among women with a TPO-ab positive status, but remained constant

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among women with a TPO-ab negative status throughout the first postpartum year. These findings suggest a link between the typical postpartum rebound phenomena of the maternal immune system and first-onset postpartum depression.

Previous studies reported a substantially higher overall risk for postpartum depression (i.e. regardless of TPO-abs status). For example, in the study of Harris and colleagues (Harris et al., 1992), 27.3% (66/242) of the women had an EDS score ≥13. In the study of Kuijpens and colleagues (Kuijpens et al., 2001), an even higher proportion of women (117/291, 40.2%) was classified with a clinical diagnosis of postpartum depression during one or more assessments (according to the RDC-criteria). This is probably due to the high proportion of women with depression in history or depression during pregnancy. In the same study, the association between an increased TPO-ab titer at 12 weeks gestation and postpartum depression remained significant after exclusion of women with an episode of depression earlier in life and/or at 12 weeks gestation (sub-analysis (n=191), OR 2.9, 95% CI 1.8-4.3). This is in in line with the odds ratio that we observed at four months postpartum (OR 3.8, 95% CI 1.3-11.6). However, in contrast to our study, Kuijpens et al. did not focus on first-onset depression since women with depression during the second and/or third trimester were not excluded. In addition, the onset timing of postpartum depression was not reported. Our study was not confounded by antenatal depression and we could therefore show evidence for a causal link between the new occurrence of thyroid autoimmunity and depression postpartum.

There is accumulating evidence that immune system dysregulation is one of the underlying biological mechanisms that play an important role in the etiology of depression (Miller et al., 2009; Osborne and Monk, 2013). A mechanism that may be specifically related to first-onset postpartum depression, is the shift from immune tolerance during pregnancy towards a pro-inflammatory state during the postpartum period (Corwin et al., 2015; Osborne and Monk, 2013). Interestingly, self-reported postpartum depression prevalence rates of the women with a positive TPO-ab status showed a pattern that is similar to the typical course of postpartum TPO-ab titers (Feldt-Rasmussen et al., 1990; Fung et al., 1988; Jansson et al., 1984; Stagnaro-Green et al., 1992): particular highly increased levels during the early (four months) postpartum period and a subsequent decrease (but still above the threshold) up to one year postpartum.

There is a well described link between the postpartum rebound of TPO-ab titers and clinical thyroid dysfunction (Lazarus et al., 2002). Consequently, among women with a positive TPO-ab status during pregnancy, first-onset postpartum depression may be related to

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a transient hypothyroid phase of postpartum thyroid dysfunction (Stagnaro-Green, 2002). Interestingly, the results of a previous study from Harris and colleagues (Harris et al., 1992) revealed that a positive TPO-ab status postpartum was predictive for an increase in depressive symptomatology postpartum, regardless of the presence of thyroid dysfunction. An explanation for this phenomenon could be that immune activation postpartum leads to increased risk of depression instead of clinical thyroid dysfunction. Interestingly, a disturbance in the suppression and activation of several T-cell subpopulations have been associated with both increased TPO-ab titers and psychiatric disorders (Bergink et al., 2013; Drexhage et al., 2011a; Drexhage et al., 2011b; Lazarus et al., 2002). Therefore, T-cell abnormalities may also play a shared role in the etiology of postpartum depression and postpartum thyroid dysfunction.

Clinical considerations

The postpartum period is known to be a trigger for first-onset psychiatric disorders (Munk-Olsen et al., 2016). In this study we were able to identify a new risk factor for the occurrence of self-reported first-onset postpartum depression at four months postpartum. The findings of the current study support the general statement that the etiology of postpartum depression is multifactorial. There seems to be a sub-group of women (especially during the first four months) in whom thyroid auto-immunity plays a role in the development of depressive symptomatology. We follow the view that thyroid function should be evaluated during the postpartum period if women present with first time depressive symptomatology. Measurement of thyroid-stimulating hormone is a first diagnostic step for the detection of thyroid dysfunction.

Another clinical consideration is the increased risk for women with increased TPO-ab titers for both thyroid dysfunction (particularly hypothyroidism) and depression later in life (Balucan et al., 2013; Pop et al., 1998; Vanderpump et al., 1995) The risk for hypothyroidism is especially high for women with both increased TPO-ab titers and TSH concentrations, even if TSH concentrations are still within the normal range (Prummel and Wiersinga, 2005; Vanderpump et al., 1995).

Strengths, limitations and directions for future research

To our knowledge, this is the first study that evaluated the association between TPO-ab titers during early gestation and (self-reported) first-onset postpartum depressive episodes. We

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included a large number of women and adjusted for potential confounders. However, our study also has several limitations. First, we did not assess TPO-ab titers, thyroid function and immune system parameters during the postpartum period. Consequently, it is unknown, to what extend thyroid dysfunction and immune system dysregulation was present among women with self-reported first-onset postpartum depression. Second, we used a self-rating questionnaire (EDS) to define depression. Therefore, it is unclear which proportion of the women with an EDS above the cut-off in our sample would fulfill the criteria of a clinically established diagnosis of postpartum depression. Third, we were not able to adjust for the presence of sexual child-abuse, which is a potential confounder of the studied association (Plaza et al., 2012). Finally, the findings of our study are not generalizable to women with a psychiatric history and/or women with antenatal depression, because we designed our study to investigate first-onset episodes of depression. Future studies on first-onset depression should also include longitudinal assessments of thyroid function (including TPO-ab titers) and immune system parameters (e.g. screening for potential abnormalities in T-cell subpopulations) during the postpartum period. This strategy will be helpful to further understand the role of immune system dysregulation in first-onset postpartum depression.

Conclusions

In this large prospective cohort study, we demonstrated that women with a positive TPO-ab status during early gestation are at increased risk for self-reported first-onset depression at four months postpartum. This period coincides with the typical postpartum rebound phenomena of the maternal immune system, which suggests an overlap in the etiology of first-onset postpartum depression and auto-immune thyroid dysfunction. Evaluation of thyroid function is essential in the clinical assessment of first-onset postpartum depression.

Author Disclosure

Contributers

RW , AK, VB and VP conceived the study. RW, AK and VP performed the analyses. RW, AK, VB and VP participated in manuscript preparation as well as in revising the manuscript. VP is the guarantor of the study. All authors have approved the final article.

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Ethics

The HAPPY-study was approved by the Medical Ethical Committee of the Maxima Medical Centre Veldhoven and the Psychology Ethics Committee of Tilburg University (protocol number EC-2012.25).

Declaration of interest

None of the authors reports any competing financial interest or conflict with the research described in the manuscript.

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Richard Wesseloo graduated as a medical doctor in 2011 and started his residency in psychiatry afterwards and now finalizing his thesis (PhD) on perinatal psychiatry. Last year, he completed his specialization in clinical epidemiology (MSc). His recent meta-analysis on postpartum relapse rates in women at high risk (Am J Psychiatry) was selected as one of the 10 clinically most important research papers in psychiatry of 2015 by the New England Journal of Medicine Journal watch.

FIGURE 1. Flow chart inclusion

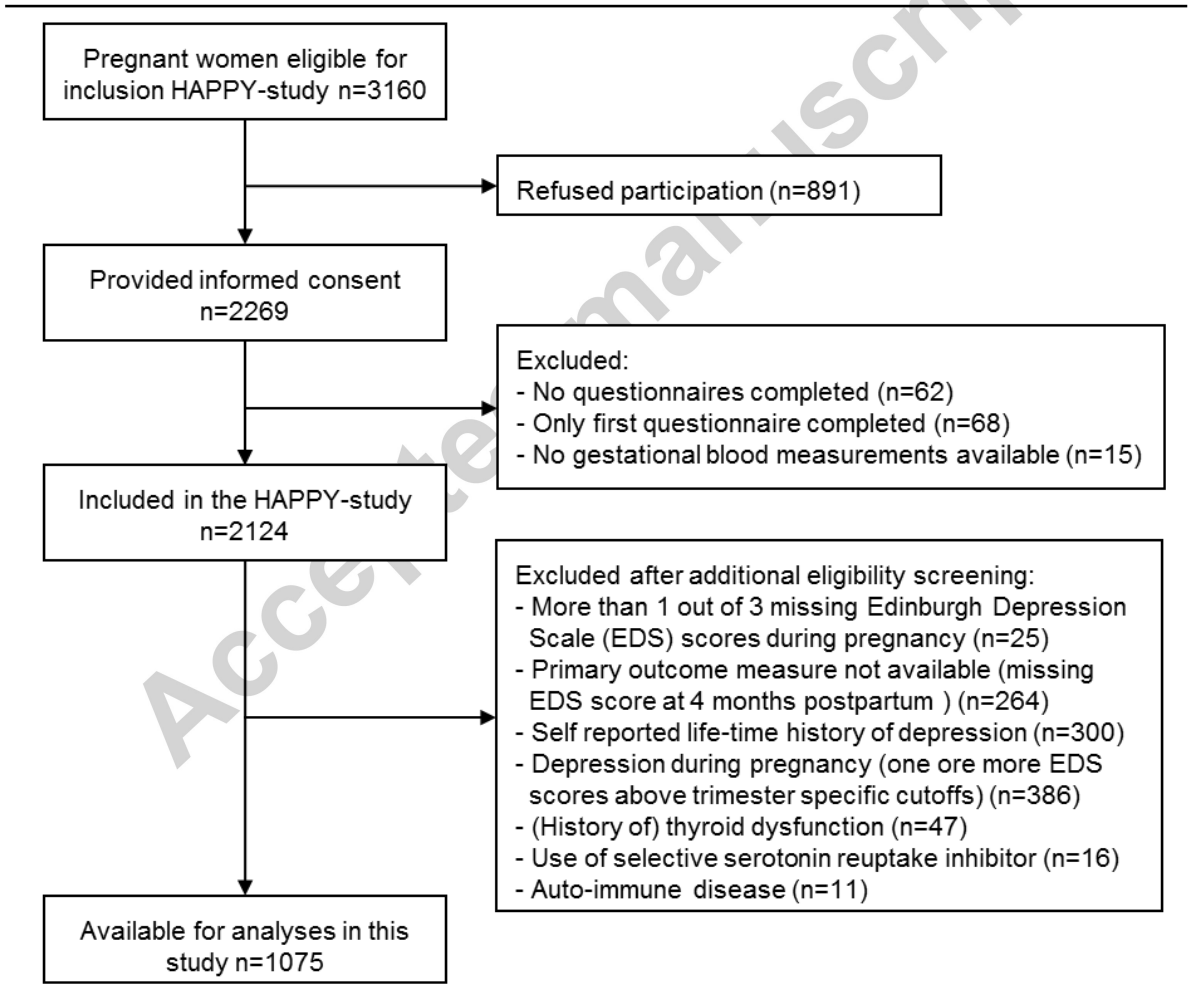

Fig. 1 Flow chart inclusion

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FIGURE 2. Point prevalence rates of postpartum depression (EDS≥13) across the first postpartum year according to TPO-ab status during pregnancy (n=1075)

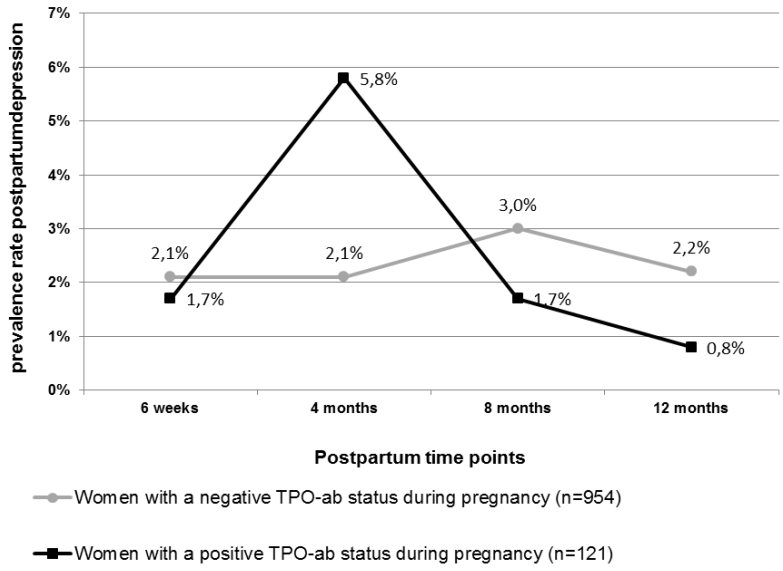

Fig. 2 point prevalence rates of postpartum depression (EDS≥13) across the first postpartum year according to TPO-ab status during pregnancy (n=1075)

Highlights

- The postpartum period triggers the new onset of both thyroid disorders and depression
- A positive TPO-ab status during pregnancy was associated with first-onset postpartum depression
- Thyroid function evaluation is essential in women with first-onset postpartum depression

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